

## REMARKS

Pursuant to this paper, claims 1-10, 12-29, 75-78, 81, 83-91, 93, 94 and 96-116 are pending in the application. Claims 11 and 95 have been canceled herein. Dependent claims 112-116 are newly added. Claims 2, 4, 15-17, 26, 29, 75-78 and 81 remain presently withdrawn as being directed to non-elected inventions or species. Thus, the claims presently under consideration include claims 1, 3, 5-10, 12-14, 18-26, 83-91, 93-94 and 96-116.

Claims 1, 23, 83, 94, 99, 100, 103 and 104 have been amended herein. The *body* of each of independent claims 1, 23, 83, 94, 99, 100, 103 and 104 is amended herein to recite that the dantrolene formulation is safe for *intravenous* administration, support for the amendment of each being found in the preambles of the claims 1, 23, 83, 94, 103 and 104 and also at page 3, l, 10-12 of the originally filed specification. Claim 1 is also amended to recite the limitation (“water-soluble surfactant”) of its now-canceled dependent claims 11 and 95. Claims 99 and 100 have also been amended to more clearly recite what Applicants consider to be the invention of those claims. Claim 104 has also been amended to correct a misspelling.

Support for new dependent claims 112-116 is found, for example, at page 19, l, 28-31 (“dantrolene sodium” limitation) and at page 21, l, 5-8 (“ready for injection” limitation) of the originally filed specification.

No new matter has been added by any of the amendments made herein.

### **1. THE AMENDED CLAIMS ARE NOVEL**

Claims 1, 3, 5-8, 10-12, 22, 95, 106, 107 and 110 were rejected under 35 U.S.C. §102(b), as allegedly being anticipated JP 5320413. (Office Action, ¶2.) Specifically, the Examiner has asserted that JP 5320413 explicitly reads on all of elements of the presently claimed invention except for the limitation “safe for injection” and that with respect to this limitation “it would have been reasonably expected that it is be [sic] safe for injection , absent evidence to the contrary” and that the burden of proof has shifted to applicants to show that the reference does not inherently possess the property “safe for injection”. (Office Action, ¶2.)

The present rejection of the claims is overcome for the following reasons.

As described in the accompanying Declaration of Dr. David M. Anderson under 37 C.F.R. §1.132 (“Anderson Declaration”), experiments performed by and under the direction of declarant unequivocally demonstrate (i) that the formulations disclosed in JP 5320413 are not

even remotely suitable for IV administration, and (ii) that the disclosure of JP 5320413 does not set forth any teaching that enables the preparation of a formulation suitable for IV administration.<sup>1</sup> The resulting particle and aggregate sizes were so large and of such abundance that any skilled worker would readily recognize that, according to art-recognized standards, they are unsafe and unsuitable for intravenous use. In fact, intravenous administration of the formulations of JP 5320413 would probably be *lethal*. Thus, JP 5320413 does not teach a “safe for injection” IV formulation and, accordingly, there is no anticipation.

In addition, to more clearly point out this distinguishing feature over JP 5320413, the body of each of independent claims 1, 23, 93, 94, 102 and 104 is amended herein to recite that the dantrolene formulation is safe for *intravenous* injection. Applicants also wish to point out that claims 19, 20, 24, 83, 84, 99 and 100 each also recite particle size limitations that, in view of the particle size analysis for formulations of JP 5320413 presented in the accompanying Declaration also clearly distinguish these claims from the prior art.

The Examiner is respectfully directed to the discussion and experimental data presented in the Anderson Declaration for further details, consideration of which is hereby requested.

In view of the above, withdrawal of the present rejection of the claims under 35 U.S.C. §102(b) is hereby requested.

## 2. THE CLAIMED INVENTION IS NON-OBVIOUS

Claims 1, 3, 5-14, 18-26, 83-91 and 93-111 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 4,543,359 to Ellis et al. (“Ellis”), in view of U.S. Patent No. 6,294,192 to Patel et al. (“Patel”), U.S. Patent No. 6,495,164 to Ramstack et al. (“Ramstack”), U.S. Patent No. 5,510,118 to Bosch et al. (“Bosch”) and JP 5320413. (Office Action, ¶¶5-8.)

The present rejection of the claims is overcome for the following reasons.

**(A.) A *prima facie* case for obviousness has not been made out because the required “reasonable expectation of success” is not present**

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<sup>1</sup> Embodiments 1,2, 4 and 5 of JP 5320413 were prepared exactly as described in that disclosure and the sizes and multiplicity/density of the resulting particles and aggregates were analyzed. Embodiment 3 was not prepared due to the lack of excipients but is similar to those prepared and tested.

The record, the accompanying and prior Rule 132 declarations and the state of the art clearly indicate that there was not a reasonable expectation of success to combine the references as the Examiner has proposed to obtain a dantrolene formulation *safe for intravenous injection*, as presently claimed. (See MPEP 2143.02, especially subsections II. and III.) Indeed, as pointed out hereinabove, the work of the Anderson Declaration demonstrates that the formulations of JP 5320413 are not suitable for intravenous injection and would likely be lethal. With respect to *Karan*, the Anderson Declaration demonstrates, contrary to the Examiner's assertion, that the formulation known as MC-D cannot be concluded to be safe for injection based on the scientific data presented in the reference. (See Anderson Declaration ¶¶12-31.) Moreover, attempts to reproduce the MC-D formulation according to the method presented in Karan resulted in thick, viscous material with very large particle size that is clearly unusable and unsafe for injection. (See Anderson Declaration ¶32.) These findings comes as no surprise since, despite an acute and continuing need for a rapidly prepared, high-concentration, intravenous-safe dantrolene formulation, 12 years later the products of the Karan reference are not in the clinic and not even under development – it is clear that they have failed. Indeed, one of the coauthors of the Karan reference, Dr. Sheila Muldoon, has confirmed that various problems existed with the MC-D formulation that caused it to fail *in vivo* testing and be discontinued. (See Declaration of Dr. Benjamin G. Cameransi ¶15.)

To wit, the state-of-the-art is that what is desired, a rapidly prepared, high-concentration, intravenous-safe dantrolene formulation, is not available and nowhere to be found except in presently claimed invention. Indeed, as Applicants previously pointed out, in view of the long felt need for such a formulation (as evidenced, for example, by Karan (1996) itself), if its preparation from a combination of the cited references were obvious, workers in the field would have long ago have produced it and brought it to the clinic given the lives that would be saved and the substantial financial reward that would be involved. No evidence supporting the existence of a reasonable expectation of success in obtaining the claimed invention by combining the cited references has been presented – instead, all of the evidence is against there being a reasonable expectation of success.

Notwithstanding the above, which is dispositive in favor of patentability, Applicants also wish to further point out that the Examiner apparently inadvertently failed to separately consider the non-obviousness of pending claims 26, 102, 106 and 107 which specifically recite a

dantrolene sodium salt formulation, since the sodium salt formulation of Karan, MC-NaD, is explicitly taught to be unsafe by the reference itself – thus, on this basis separately, there could be no reasonable expectation of success to achieve a rapidly prepared, high-concentration, intravenous-safe dantrolene sodium formulation. Applicants also wish to point out that new dependent claims 112-116 specifically recite that the dantrolene formulation is sodium dantrolene and is constituted “ready for injection” which further advantageously and patentably distinguishes the invention of these claims from the MC-D formulation of Karan which is not constituted ready for injection but which, as Karan itself states, requires filtration.

**(B.) The particle size parameter is not a mere optimization of a parameter but is a critical, inventive aspect of the present invention**

The Examiner erred in considering the particle size parameter of the presently claimed invention to be a mere optimization. (Office Action, p. 5, l. 8-10.) Particle size of a colloidal formulation cannot simply be conjured and implemented at will. The size parameter is unpredictable here because, among other reasons, of the propensity of colloidal particles to combine and aggregate. By contrast, in *In re Boesch*, 205 USPQ 215 (CCPA 1980), on which the Examiner has improperly relied, the issue was optimizing the proportion of particular metals in an alloy, parameters that are 100% predictable, controllable and not subject to change spontaneously.

As pointed in the accompanying Anderson Declaration, in recreating and testing the formulations of JP 5320413 it was shown that only formulations having particles far too large for safe intravenous administration were obtained. This shows that the Examiner’s assertions of the triviality of obtaining intravenous safe formulation and the interchangeability of oral and intravenous formulations are not correct. Moreover, as further pointed out in the accompanying Anderson Declaration, a particle size sufficiently small that is stable for use of the intravenous injection formulation is critical *to the survival of the patient*. Thus, this parameter is critical and is neither predictable nor obtainable by merely reading the cited prior art.

**(C.) The asserted rejection employs an improper degree of hindsight**

Even assuming, *in arguendo*, that the cited references contain the various elements needed to construct the presently claimed invention, the degree of picking-and-choosing required

to make the invention is so extreme that no skilled worker would be so guided without the benefit of the present disclosure. While the Courts have suggested that *some* degree of hindsight is permissible in making a finding of obviousness, Applicants respectfully submit that an extreme and impermissible degree of hindsight relying almost exclusively on the guidance provided by the instant specification has been employed, and would have to be employed, to selectively pick out the disparate steps cited from the recited references and arrange them in a manner approximating the presently claimed invention. How would any skilled worker know or be guided to create the particular formulation of the presently claimed invention based only on the references? It is not enough for obviousness that among thousands of possible permutations of combinations of elements from numerous references may lay a claimed invention. Indeed, given the teachings of the cited references a skilled worker would not be guided to the presently claimed invention over any other of the multitude of permutations.

**(D.) The alleged obviousness of the presently claimed invention is rebutted by evidence of long felt need for the invention which has not been previously satisfied**

The Examiner rejected Applicants' prior assertion of rebuttal of the alleged case of obviousness based on satisfying a long-felt unmet need as allegedly failing to show evidence of prior unsuccessful attempts and, moreover, as allegedly addressing a need that has already been met in the art, namely by formulation MC-D of the Karan reference and the formulations of JP-5320413. (Office Action, ¶¶12-17.) In response, Applicants now submit and refer to objective evidence showing that the prior attempts were, in fact, unsuccessful, and that the referenced long felt need has not been previously met. As also discussed in subsection (A.) above, the Anderson Declaration clearly shows that the formulations of JP 5320413 were unsafe for injection and both the Anderson and Cameransi Declarations show that formula MC-D and MCNaD of Karan were unsafe for injection. Therefore, the only attempts of record, those of Karan and JP 5320413, were unsuccessful attempts that did not meet the need for a high-concentration, safe for injection dantrolene formulation. This is the second of the three prongs of the test for long-felt need cited by the Examiner. (at ¶14 of the Office Action.)

To briefly address the two other prongs of the test, as pointed out at ¶13 of the Office Action, first the need must have been a persistent one that was recognized by those of ordinary

skill in the art. The Karan (1996) reference itself clearly supports that the need for a high-concentration, safe for injection dantrolene formulation has been longstanding, which is further supported by each of the Rule 132 Declarations of Brandom (e.g. ¶¶11) and Cameransi (e.g. ¶¶4 and 15(g)). As pointed out at ¶15 of the Office Action, the third prong of the test requires that the claimed invention must in fact satisfy the long-felt need. This prong is clearly shown to be satisfied by the Brandom Declaration and, in particular, Gerbershagen et al. (2007) Comparison of Therapeutic Effectiveness of Dantrolene and Ryandodex in Porcine Malignant Hyperthermia, Anesthesiology 107: A1922 (Exh. to Brandom Dec.; also submitted in IDS), discussed therein. Thus, all three prongs required to rebut the alleged *prima facie* case of obviousness on the basis of satisfying a long felt need have been met and the Examiner is therefore respectfully requested to accord patentable weight to the claims on this basis.

In view of the above, Applicants respectfully request withdrawal of the present rejections of the claims under 35 U.S.C. §103(a).

### 3. CONCLUSION

Applicants respectfully submit that pending claims 1-10, 12-29, 75-78, 81, 83-91, 93, 94 and 96-116, of this application, which are presently under examination, are in condition for allowance. Prompt and favorable reconsideration and allowance of all pending claims is respectfully requested. The Examiner is invited to contact the undersigned to discuss any matter in this application.

Pursuant to 37 C.F.R. §1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. It is believed that no fees other than those paid concurrently are due in connection with the filing of this paper. However, should it be deemed that any other fee is due in connection with this paper, authorization is hereby given to charge such fee to Deposit Account No. 02-2275.

Respectfully submitted,

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